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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,268	10/05/2001	Peter R. Baum	3101-A	4855

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 03/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/972,268	BAUM ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-111* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59-111* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 12/03/04, is acknowledged.

2. Claims 59-111are pending and under consideration.

3. Claim 102 is objected to because it is missing a period at the end of the claim.

4. In view of the amendment filed on 12/3/05, only the following rejections are remained.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 60 and 67 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrases: "extending from amino acid 58 through the C-terminus of SEQ ID NO:15" claimed in claim 60(c), lines 7-8, and "extending from amino acid 58 through the C-terminus of SEQ ID NO:16" claimed in claim 67(c), lines 7-8, represent a departure from the specification and the claims as originally filed for the same reasons set forth in the previous Office Action mailed 6/04/04.

Applicant's arguments, filed 12/03/04, have been fully considered, but have not been found persuasive.

Applicant directs particular attention to the specification on page 17, lines 14-17, page 14, lines 27-31 and page 5, lines 18-24 for support for claimed limitation. In particular, the specification on page 17 discloses SEQ ID NO: 15 and 16 are the amino acid sequences of the extracellular domains of nectin-3α and nectin-3β, respectively, fused at their C termini to a FLAG® peptide sequence (amino acids 405 through 420 of SEQ ID NO: 15 and amino acids 366 through 381 of SEQ ID NO: 16) and a C-terminal polyHis stretch of six histidine residues. The specification on page 14 discloses that the mature form of nectin 3α and nectin 3β form is from amino acid residue X1 to amino acid 549 and 510, respectively, wherein X1 is an amino acid between and including residues 51-58. Wherein the specification on page 5 discloses that the extracellular domain of nectin-3α extends to amino acid 404 of SEQ ID NO:6 and the extracellular domain of nectin 3β extends to amino acid residue 365 of SEQ ID NO:12.

However, the specification on page 5, lines 18-24 discloses that the extracellular domain of nectin-3α (including the signal sequence) extends from an amino acid between 1 and 39 through approximately amino acid 404 of SEQ ID NO: 6 (e.g., from about x1 to 404, wherein x1 is an amino acid between 1 to 39). The extracellular domain of nectin-3β extends from an amino acid between 1 and 39 through approximately amino acid 365 of SEQ ID NO: 12 (e.g., from about x1 to 365, wherein x1 is an amino acid between 1 and 39).

Further, obviousness is not the standard for the addition of new limitations to the disclosure as filed. It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977). New Matter is a written description issue.

7. Claims 59-111 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a substantially purified polypeptide comprising an amino acid of SEQ ID NO: 2, 4, 6, 8, 10, 12 and 31, wherein SEQ ID NO:4, 6, 10, 12, and 31 comprising amino acids 74-152, 189-250 and 287-342, and SEQ ID NO: 13-16, wherein the polypeptide consists of amino acid sequence that binds to nectin-1 for inhibiting endothelial cell migration; does not reasonably provide enablement for any substantially purified polypeptide comprising amino acids 58-404 of SEQ ID NO:4 or 6, in claim 59, wherein said polypeptide comprises any amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:2 or 6, 13, 15 in claim 60; Any substantially purified polypeptide comprising amino acids 74 through 635 of SEQ ID NO: 10, 12 or 31 in claim 66, wherein said polypeptide comprises any amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NOs:10, 12, 14, 16, or 31 in claim 67; any substantially purified polypeptide comprising any amino acid sequence selected from the group consisting of amino acids 58-342 of SEQ ID NO:4, 6, 10, or 31, amino acids 74-342 of SEQ ID NO:4, 6, 10, 12 or 31, amino acids 74-342 of SEQ ID NO:4, or 6 and amino acids 74-365 of SEQ ID NO:10, 12, or 31 in claim 73; any substantially purified polypeptide comprising any amino acid sequence that inhibits endothelial cell migration and that shares at least 80% amion acid identity across the length of amino acids 58-404 of SEQ ID NO:4 or 6 in clai 79, wherein said polypeptide comprises an amino acid sequence sharing 85%, 90%, 95% or 99% amino acid identity across the length of amino acids 58 through 404 of SEQ ID NO: 4 or 6 in claim 80; any substantially purified polypeptide comprising an amino acid sequence that inhibits endothelial cell migration and that shares at least 80% amino acid identity across the length of amino acids 74 through 365 of SEQ ID NO:10, 12 or 31 in claim 86, wherein said polypeptide comprises an amino acid sequence sharing 85%, 90%, 95%, or 99% amino acid identity across the length of amino acids 74 through 365 of SEQ ID NO:10, 12 or 31 in claim 87; any substantially purified polypeptide comprising an amino acid sequence that inhibits endothelial cell migration and that shares at least 80% amino acid identity across the length of a contiguous amino acid sequence comprising amino acids 74 through 152 and 189 through 250 of SEQ ID NO:4, 6, 10, 12 or 31 in claim 93, wherein said polypeptide comprises an amino acid sequence sharing 85%, 90%, 95% or 99% amino acid identity across the length of a contiguous amino acid sequence comprising amino acids 74 through 152 and 189 through 250 of SEQ ID NO:4, 6, 10, 12, or 31 in claim 94; any isolated polypeptide of claim 93 produced by a process comprising (a) culturing a recombinant host cell comprising any "polynucleotide" having

nucleotide sequence encoding said polypeptide and (b) isolating said polypeptide in claim 100, wherein said polypeptide is produced by a process comprising culturing a recombinant host cell comprising a polynucleotide having a nucleotide sequence encoding said polypeptide or The polypeptide of claim 100, wherein said polypeptide is produced by a process comprising culturing a recombinant host cell comprising any polynucleotide having any nucleotide sequence encoding said polypeptide, wherein said nucleotide sequence is selected from the group consisting of nucleotide4s 172-1026 of SEQ ID NO:3, 5, 9 or 11; nucleotides 172-1212 of SEQ ID NO:3 or 5, and nucleotides 172-1098 of SEQ ID NO: 9 or 11 in claim 102; wherein said polypeptide comprises an amino acid sequence selected from the group consisting of (a) amino acids 58-342 of SEQ ID NO: 4, 6, 10, 12 or 31, (a) amino acids 58-404 of SEQ ID NO:4 or 6, (c) amino acids 74-342 of SEQ ID NO:4, 6, 10, 12 or 31, (d) amino acids 74-404 of SEQ ID NO:4 or 6, (e) amino acids 58 through 365 of SEQ ID NO:10, 12, or 31 and (f) amino acids 74-365 of SEQ ID NO:10, 12 or 31 in claim 105, wherein said polypeptide is produced by a process comprising culturing a recombinant host cell into which a polynucleotide comprising a nucleotide sequence encoding said polypeptide has been introduced in claim 111. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action mailed 6/04/04.

Applicant's arguments, filed 12/03/04, have been fully considered, but have not been found persuasive.

Applicant argues in conjunction with case law, regarding the term "comprising", which is open-ended and expands the claimed sequences to include additional non-disclosed amino acids on either or both sides of the N-and C-terminal of the polypeptide, that "comprising" is a term of art used in claim language, which means that the named elements are essential, but that other elements may be added and still form a construct within the scope of the claims. Applicant submits that the specification has fulfilled the requirements for enablement by teaching throughout the specification how to make and use polypeptides comprising this "essential element" that would fall within the scope of the claimed invention. Applicant further asserts that the specification also teaches how to make embodiments that would fall within the scope of the claimed invention. These include but are not limited to, N- or C terminal fusions (page 8, and examples 3 and 4 for the tagged extracellular domain used in the assays), fusions joined by peptide linkages, fusions derived from immunoglobulins such as Fc and other embodiments which were known in the art at the time of filing the present application. Applicant points to Example 4 which teaches that a soluble nectin3Fc fusion protein comprising amino acid residues 58-404 of SEQ ID NO:6 binds strongly to nectin 1 transfected cells. Applicant submits in conjunction with case law that it is not necessary to recite every possible embodiment in order to fulfill the requirements of enablement. Applicant maintains that the instant application provides sufficient teaching to allow one of skill to make and use the embodiments encompassed by the scope of the claims.

However, the Examiner's position is that the term "comprising" leaves the claims open for the inclusion of unspecified amino acids on either or both sides of the N- and C-terminal of the core structure of nectin 3 polypeptide. See MPEP 2111.03. The specification fails to provide sufficient guidance as to which amino acids outside the core structure of SEQ ID NO: 4 and 6 is essential for maintain its nectin 1 binding activity and which amino acids can be added to the core structure of SEQ ID NO: 4 and 6 and still maintained the same function, besides the full length SEQ ID NO: 2, 4, 6, 8, 10, 12, and 31. The claims fail to meet the enablement requirement for the "how to make" prong of 35 U.S.C. 112, first paragraph: Since the instant fact pattern fails to indicate that a representative number of structurally related compounds is disclosed, the artisan would not know the identity of any non-disclosed compound failing within the scope of the instant claim and consequently would not have known how to make it.

With respect to claims 79-111, applicant traverses the rejection on the ground of undue experimentation and quantity of experimentation, MPEP 2164.06. Applicant submits that the previous Office Action provides no evidence that the speculated experimentation, if even necessary, would be beyond that which is routine to one of skill in the art. Applicant asserts that the specification teaches a multitude of methods used in the art to make and use the sequences of the calimed invention. For example, percent identity can be determined either visually or mathematically. Various art recognized computer programs and algorithms as well as a table of percent identities for human nectins that were generated using such algorithms are provided, (page 16, 1st paragraph). Applicant submits that many of those tools are readily available via the internet and are known and used by those skilled in the art. Applicant submits that methods for the production of polypeptides, via recombinant expression or known conventional chemical synthesis, which are known and practiced in the art are described, for example, at page 22, last paragraph. Applicant further, submits that numerous assays for identifying and characterizing the function of the claimed sequences are known in the art and are provided on pages 36-40. Assays related to endothelial cell migration are exemplified in the specification, in particular in the paragraph bridging pages 36-37 and Example 4 and 5. Applicant points to pages 6-10 and tables 2-3, where the identification of positions in the protein that are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions are disclosed.

Again, in order to satisfy the U.S.C 112, 1st paragraph, the specification has to teach how to make and use the invention, not how to identify the invention. Until the time when at least about 80%, 85%, 90%, 95% or 99% sequence identity polypeptides are found, then one skill in the art can make them. Since the core structure of the nectin 3 polypeptides is a key determinant of activity of nectin 3, residue substitutions that are conservative can have severe phenotypic effects. However, there is no simple way to infer the likely effect of an amino acid substitution on the basis of sequence information alone. Further, it is recognized in the prior art that the function of a protein depends on the sequence of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence and the functional properties of the different parts of the protein. The specification does not teach which changes in the amino acid

of SEQ ID NOs: 4, 6, 10, 12, 31 would not alter all the activities of the polypeptides. Therefore, the specification fails to provide sufficient guidance as to which amino acid of SEQ ID NOs: 4, 6, 10, 12, 31 is essential for maintain its biological activity and which changes can be made in the structure of SEQ ID NOs: 4, 6, 10, 12, 31 and still maintained the same function.

Applicant is relying upon certain biological activities and the disclosure of three species to support an entire genus. The claims as written encompass a broad genus of polypeptides with an unlimited number of possibilities with regard to the length and variation of the polypeptide sequence. Further, the enablement issues of making the protein still remain because the specification does not teach and provide sufficient guidance as to which amino acid in the core structure of SEQ ID NO: 4, 6, 10, 12, 31 would have been altered such that the resultant polypeptide would have retained the function of inhibiting endothelial cell migration. In addition, variation up to 20% in the core structure of SEQ ID NO: 4 or 6 ($79^{20} = 8.97\ 10^{37}$ variation) provide a range of activities, not all which are necessarily predictive of inhibiting endothelial cell migration. While experimental testing techniques using cell adhesion compounds are available, it is not routine in the art to use such methods when the expectation of success is unpredictable based on the instant disclosure. Thus, it would require an undue amount of experimentation of one skilled in the art to practice the invention as broadly claimed.

As for Skolnick, Metzler and Martinez references, Applicant submits that the previous action has not addressed the issues raised by Applicants that when each reference is read as a whole that none of the cited references can be considered to teach an inability of the skilled artisan to predict the functionality of nectin polypeptide variants from their amino acid sequence, especially when nectin-3 function has already been experimentally established.

Contrary to Applicant assertions, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). Thus, Skolnick et al teach provide evidence that existing functional annotation methods is fraught with inaccuracies and that theses methods are still notably deficient in defining and describing the complexity of protein function. Therefore, even though the overall similarity of the structure of nectin-3 polypeptides with other nectin polypeptides: the three Ig domains, the transmembrane domain, and the similarity of sequences at the intracellular C-terminus that are seen in the members of the nectin polypeptide family only experimental research can confirm the artisan's best guess as the function of the structural related protein. Further, the claims encompass alterations in protein folding because claims do permit deviation from the amino acid sequences of the consensus regions for a non-native protein. It would be reasonable to conclude that alterations in protein folding would lead to a large alteration in binding affinity of nectin-3 with nectin-1.

8. Claims 59-78 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action, mailed 6/4/04.

Applicant is in possession of a substantially purified polypeptide comprising an amino acid of SEQ ID NO: 2, 4, 6, 8, 10, 12 and 31, wherein SEQ ID NO:4, 6, 10, 12, and 31 comprising amino acids 74-152, 189 to 250 and 287 to 342, and SEQ ID NO:13-16 wherein the polypeptide consists of amino acid sequence that binds to nectin-1 for inhibiting endothelial cell migration.

Applicant is not in possession of any substantially purified polypeptide comprising amino acids 58-404 of SEQ ID NO:4 or 6, in claim 59, wherein said polypeptide comprises any amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:2 or 6, 13, 15 in claim 60; Any substantially purified polypeptide comprising amino acids 74 through 635 of SEQ ID NO: 10, 12 or 31 in claim 66, wherein said polypeptide comprises any amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NOs:10, 12, 14, 16, or 31 in claim 67; any substantially purified polypeptide comprising any amino acid sequence selected from the group consisting of amino acids 58-342 of SEQ ID NO:4, 6, 10, or 31, amino acids 74-342 of SEQ ID NO:4, 6, 10, 12 or 31, amino acids 74-342 of SEQ ID NO:4, or 6 and amino acids 74-365 of SEQ ID NO:10, 12, or 31 in claim 73.

Applicant's arguments, filed 12/03/04, have been fully considered, but have not been found persuasive.

Applicant traverses the rejection on the ground that the specification describes the claimed polypeptides and their functional properties in sufficient detail as to convey to one of skill in the art that Applicants were in possession of the invention at the time of filing. Applicant refers to the Examination Guidelines set forth by the USPTO, on written description requirement for a claimed genus may be satisfied by the description of a representative number of species or the disclosure of relevant identifying characteristics sufficient to show the Applicants were in possession of the claimed genus.

However, there is no described or art-recognized correlation or relationship between the structure of the invention, the core structure of nectin 3 and it's inhibition of endothelial cell migration function, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of polypeptides comprising the core structure of nectin 3 which retain the features essential to the instant invention.

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).
March 8, 2005

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